REVIEW ARTICLE



EFFECTS OF MUSCLE STRENGTHENING AND CARDIOVASCULAR FITNESS ACTIVITIES FOR POLIOMYELITIS SURVIVORS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: To evaluate and assess the effectiveness of muscle strengthening and cardiovascular interventions in improving outcomes in poliomyelitis (polio) survivors.

Data sources: A systematic literature search was conducted in Medline, PubMed, CINAHL, PsychINFO, Web of Science, and Google Scholar for experimental and observational studies.

Study selection and extraction: Screening, dataextraction, risk of bias and quality assessment were carried out independently by the authors. The quality appraisal and risk of bias were assessed using the Downs and Black Checklist. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed to increase clarity of reporting.

Data synthesis: A total of 21 studies that met all the inclusion criteria were subjected to statistical analyses according to intervention (muscle strengthening or cardiovascular fitness). A random-effects meta-analysis showed a statistically significant effect for the exercise interventions favouring improvement in outcomes according to the International Classification of Functioning, Disability and Health (ICF).

Conclusion: This review provides further insight into the effects associated with muscle strengthening and cardiovascular interventions among polio survivors, and helps to further identify the current state of research in this area. Future research is needed, focusing on individualized approaches to exercise with polio survivors and specific exercise prescription recommendations, based on established frameworks, such as the ICF.

Key words: post-polio syndrome; International Classification of Functioning, Disability and Health framework; exercise-based intervention; rehabilitation.

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Poliomyelitis (polio) is a highly infectious, viral disease that affects the nervous system and can cause total paralysis (1). Based on published records, the World Health Organization (WHO) estimates there

LAY ABSTRACT

Polio survivors are an ageing population and prone to functional decline. Multiple age-related diseases affect this population, in addition to Late Effects of Polio (LEoP). Exercise plays an important role in improving strength and overall cardiovascular fitness in these individuals, and clinicians face challenges when advising polio survivors on the optimal level of exercise to avoid producing pain and/or fatigue. Improvements in strength and cardiovascular fitness have the potential to translate into activities of daily living within this cohort. To our knowledge, this is the first systematic review and meta-analysis using a broad approach (i.e. including both experimental and observational studies) to capture and summarize the research to date regarding the role of muscle strengthening and aerobic conditioning exercise in polio survivors. This review provides valuable information for clinicians, which will help enable the development of specific exercise prescription appropriate to this population.

are 20 million polio survivors worldwide (1). Although outbreaks of polio have reduced significantly as a result of vaccination, 15–80% of all polio survivors develop post-polio conditions (2). Post-polio syndrome (PPS) is a clinical diagnosis in which symptoms may become apparent 15–30 years after exposure to polio (3, 4). PPS is characterized by progressive or new muscle weakness, generalized fatigue, muscle atrophy and pain (4, 5). Internationally, the cluster of signs and symptoms that include PPS features and additional biomechanical symptoms is referred to as Late Effects of Polio (LEoP) (6).

PPS can lead to significant disability, including inability to work, loss of mobility and loss of independence (4). Many individuals with PPS report being inactive, due to weakness and fatigue; symptoms that are perceived to worsen with activity (4). Reduced physical activity associated with muscle atrophy and deconditioning can then potentiate further fatigue and weakness and be linked with reduced muscle capacity and cardiovascular fitness, probably contributing to higher comorbidity rates and potential hospitalization (7). Aerobic fitness intervention modalities, such as walking, cycling, arm ergometry and water-based exercise, have been shown to be effective in attenuating

decline in function in patients with PPS (8, 9). Furthermore, muscle strengthening training can also increase functional capacities in individuals with PPS (5), with previous research reporting improvements in isometric and isokinetic strength in individuals with PPS (4).

A recent systematic review initially raised concerns that polio survivors might overload weak muscles during exercise, causing an increase in symptoms, such as pain. fatigue and weakness (5). Despite this common concern, based on the methods used in this review. limited evidence was found to substantiate this (5). Earlier, a 2008 meta-analysis, limited by the number and quality of included studies, showed some cardiovascular outcomes could be improved in polio survivors, but apparent positive effects of strengthening were not significant (10). Such conflicting recommendations may cause clinicians and polio survivors to experience concerns about further risk of adverse outcomes when considering whether to pursue exercise programmes (8). The management of PPS symptoms is essential for maintaining quality of life and independence (11, 12). The benefits of exercise for those with non-communicable diseases comparable to PPS include improvements in productivity and wellbeing, and reduction in health system expenditure, further identified in a recent study focused around the role of the clinical exercise physiologist (13).

Clinicians can experience uncertainty when advising polio survivors on exercise, as divergent results and recommendations exist (10, 14). Limited modes of exercise have been studied in the literature with regard to this population, but aspects of exercise have been sufficiently tested to prompt this review. This systematic review and meta-analysis aims to summarize current knowledge of the effectiveness of muscle strengthening and cardiovascular interventions (and/or mixed interventions including both) in improving outcomes in polio survivors. The main hypothesis of this study is that these exercise interventions will improve outcomes in polio survivors above and beyond usual practice.

METHODS

Search strategy

The following computerized databases were searched for articles published from their respective inception dates to 20 February 2020, inclusive: Medline, PubMed, CINAHL, PsycINFO, Web of Science, and Google Scholar. Search terms were mapped to MeSH terms, or subject headings and synonyms were grouped together using Boolean operators. A range of search terms were used to identify the population, exercise interventions, and outcomes (see Table SI¹). Both experimental (e.g. randomized controlled trials; RCTs) and observational (e.g. cohort studies)

study designs were included in the search strategy and inclusion criteria. Results of the database searches were downloaded into Endnote X8 (Clarivate, Philadelphia, US) and duplicate papers were excluded. One author (AR) screened citation titles and abstracts for potentially relevant titles and abstracts. Article full-text versions were then screened (AR and TL). Disagreements were resolved by consensus with the 2 remaining authors. Reference lists of all studies assessed against the eligibility criteria were also screened for additional literature.

Inclusion and exclusion criteria

Articles were included if: (*i*) the study targeted a sample of participants experiencing LEoP or PPS following a period of stable neurological function after 15 years; (*ii*) the focus was on original research; (*iii*) an exercise intervention was used; and (*iv*) publication was after 1980. Studies were excluded if they were: (*i*) conference or poster presentations; (*ii*) not original research; or (*iii*) not in English. Studies were not restricted by study design.

Quality assessment and risk of bias

Two independent reviewers (AR and TL) assessed the quality of the included studies using Downs and Black checklist (15) (Table SII1). The checklist consists of 27 questions addressing study reporting, external validity, internal validity (bias, confounding) and power. The quality index of the checklist has high criterion validity (r=0.90), high internal consistency (KR-20=0.89), test-retest (r=0.88) and inter-rater (r=0.75) reliability. For dimension reduction purposes, these items were reduced to 17 questions, with each question coded as either "yes", "no", or "undetermined". The sum of each "yes" response contributed to the overall quality score, where higher scores indicate greater methodological quality. High-quality studies were categorised as 85–100%, moderate quality studies as 60–84%, and low quality as less than 59% (15). Two authors (AR and TL) rated each article independently. All disagreements (n=15; 4% of all questions) were discussed at a consensus meeting and appropriate ratings decided on by the remaining authors.

Level of evidence

According to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework (16), the quality of evidence in this review can be utilised to help make recommendations to clinicians and polio survivors. Hence, based on risk of bias, inconsistency, indirectness, imprecision and other considerations, a summary of findings table was produced (Table I), highlighting overall certainty as well as the clinical importance of each key domain outcome.

Data extraction

The following data were extracted from included studies: author, study population, diagnosis criteria used, study design, follow-up time, type of exercise intervention, outcome measures, statistical analysis, and effects of the intervention. The International Classification of Functioning, Disability and Health (ICF) codes provide a framework for understanding the interactions of environment, conditions and personal factors on influencing body function and structure, activities and participation (17). Table SIII¹ outlines second-level domain coding of the ICF for study outcome measures. Based on a proposed ICF Core Set for PPS (17), outcomes were grouped into the following ICF domains: body function component (1) muscular; (2) cardiovascular;

¹http://www.medicaljournals.se/jrm/content/?doi=10.2340/16501977-2832

Table I. Summary of findings based on outcome domains and study design

Certainty ass								
Nr studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Impact	Certainty
Activity and Pa	articipation (follo	w up: range 3	weeks to 15 mont	hs)				
2/6 ^a	randomised trials and observational study designs	not serious	not serious	not serious	not serious	all plausible residual confounding would suggest spurious effect, while no effect was observed	RCTs: Koopman et al. (3) and Murray et al. (4): Consistency in methods, interventions and outcomes (e.g. 6MWT, 2MWT, TUG), CIs considered not wide, homogenous. Observational: Bertelsen et al. (28), Brogardh et al. (46), Da Silva et al. (37),	RCT only: ⊗⊗⊗⊗ HIGH All study designs: ⊗○○○ VERY LOW
							(40), ba slive et al. (29), Sharma et al. (32), Skough et al. (38), Willen et al. (8): Some consistency in methods and activity outcomes. Interventions varied: strengthening, CV fitness, mixed, CIs considered not wide, homogenous.	
			: range 4 weeks to					
3/5	randomised trials and observational study designs	serious ^c very serious _{b,c}	not serious serious ^d	not serious serious ⁹	not serious serious ^h	all plausible residual confounding would suggest spurious effect, while no effect was observed	RCTs: Koopman et al. (3), Oncu et al. (48) and Murray et al. (4) some consistency in methods, interventions and outcomes (e.g. all fatigue), CIs considered not wide Observational: Bertelsen et al. (28), Da Silva et al. (37), Davidson et al. (29), Dean et al. (25), Sharma et al. (32): Varied effect, CIs not wide, apparent improvement, interventions similar but outcomes varied.	RCT only: ⊗⊗⊗○ MODERATE All study designs: ⊗○○○ VERY LOW
Body function	lower (follow up	: range 16 we	eks to 10 months)					
2/9	randomised trials and observational study designs	very serious ^{b,c}	serious ^d	not serious	serious ⁿ	publication bias strongly suspected, all plausible residual confounding would suggest spurious effect, while no effect was observed ⁱ	Jones et al. (47), Koopman et al. (3): Varied effect, wide CIs, apparent improvement, similar study characteristics (methods, interventions and outcomes).	All study designs: ⊗○○○ VERY LOW
Body function 4/2	randomised	tollow up: rang very	ge 8 weeks to 10 m serious ^d	onths) serious ^{f,g}	serious ^h	all plausible residual	lones et al. (47). Kriz et al.	All study
4/2	trials and observational study designs	serious ^{b,c}	serious-	serious	serious.	confounding would suggest spurious effect, while no effect was observed ⁱ	Jones et al. (47), Kriz et al. (26), Koopman et al. (3), Oncu et al. (48): Varied effect, wide CIs, apparent improvement.	designs:
	•		weeks to 16 weeks					
3/2	randomised trials and observational study design	very serious ^{b,c,d}	serious ^e	serious ^{f,g}	serious ^h	all plausible residual confounding would suggest spurious effect, while no effect was observed ⁱ	Murray et al. (4), Chan et al. (33), Kriz et al. (26): Varied effect, wide CIs, apparent improvement.	All study designs: ⊗○○○ VERY LOW

^aindicates ratio of RCT to non-RCT studies. CI: Confidence interval, CV: Cardiovascular fitness, RCT: randomised controlled trials, TUG: Timed up and go test, 6MWT: Six min walk test, 2MWT: Two min walk test Explanations: ^bno measure of random variability ^climited adjustment of confounding ^dlimited loss to follow-up, no intention to treat analysis ^esubstantial heterogeneity ^fDifferences in diagnostic criteria ^gDifferences in outcome measures ^hWide Confidence Intervals ⁱas identified via funnel plot

(3) mental and sensory; and as a dual component domain (4) activity and participation.

As outlined in Table SIII¹, the muscular function domain contains outcome measures such as isometric and dynamic strength, the cardiovascular domain contains outcome measures such as peak oxygen uptake, heart rate, blood pressure, and aerobic capacity (VO₂) and mental and sensory domain contains pain and fatigue. The activity and participation domain contains outcome measures (from activities) such as 6-min walk test, 6-min arm test, Timed Up and Go test, 10-metre walk test, 2-min walk test, and (from participation) such as daily physical activity level scale for people with disabilities, Short-Form 36 (SF-36), physical component summary, mental component summary.

Data analysis

Following data extraction, effect sizes and their corresponding 95% confidence intervals (95% CI) were derived for each individual outcome. In the event multiple outcomes denoted a given ICF domain or component, a representative effect size was calculated by pooling the effect size of each outcome using Comprehensive Meta-analysis v3 (BioStat, Englewood, NJ USA). Data were sub-grouped into the respective interventions used (aerobic fitness, mixed, and muscle strengthening) and meta-analyses were completed on the combined body function domain, and each of its underlying components (lower limb, non-lower limb, cardiovascular, and mental and sensory), and a collated activity and participation domain. For all analyses, a

generic inverse variance, random effects model was used. This model was adopted due to the anticipated differences among studies (study duration, outcome measures, and/or post-polio condition severity). Effect sizes were reported as Hedges g. with the magnitude of the effect defined using standardized conventions, where small, moderate, and large are represented by values of 0.20, 0.50, and 0.80, respectively (18). Significance was investigated through the use of p-values, where the alpha was set at ≤ 0.05 . Heterogeneity was evaluated using Cochran's O, where the alpha was set at ≤ 0.10 . In the event significance was reported, the I2 statistic was then explored to define the magnitude of heterogeneity about the result, where 0-40, 30-60, 50–90, and 75+ were suggestive of low, moderate, substantial, and considerable heterogeneity, respectively (19). Leave-oneout sensitivity analyses were conducted when statistical heterogeneity was reported. In order to investigate the effects of intervention duration on the domains and/or components of the ICF, meta-regression was performed at the study level using a random-effects model. Publication bias was also investigated statistically through the Begg and Mazumdar's rank correlation test and Eggers linear regression model, which were applied to each component and the overall analyses. If publication bias was detected, Duval and Tweedie's trim and fill correction was applied and the resultant Hedges g and associated 95% CI were explored. Given the software used for these analyses the L_o estimator was used to formulate the correction. GRADEPro GDT (20) (McMaster University, Hamilton, Ontario, Canada)

was used to develop a summary of findings table consistent with the GRADE handbook (16).

RESULTS

Systematic search and study quality

Fig. 1 shows the flow diagram of the systematic search, consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (21). The search strategy produced 2,644 citations from 6 databases. Following the removal of duplicates, 2,327 studies remained. After title and abstract screening, 48 studies were then assessed against the eligibility criteria, where 21 citations were then included and assessed for study quality, with the quality assessment scores ranging from 53% to 88%. The mean (standard deviation (SD)) score of study quality was found to be 72.5 (10.5) %. Individual scores for each study are also shown in Table SIII1. Of those studies satisfying study quality, there were 2 instances where more than one article was based on the same sample (3, 9, 22, 23), with the latter also examining both iso-

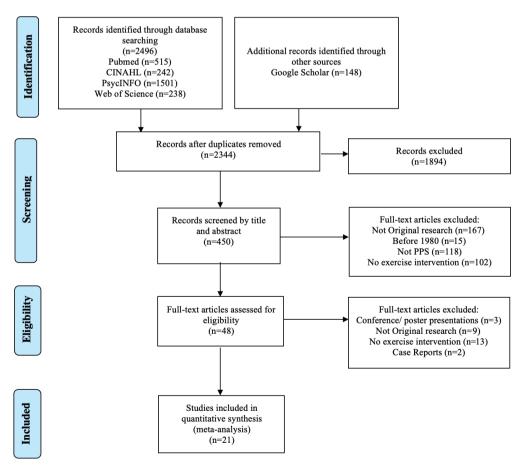


Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (21) flow diagram outlining the identification and inclusion process for the quantitative review. PPS: post-polio syndrome.

metric and isokinetic exercise. Hence, the latter study in each circumstance of overlapping samples was removed from the analysis. Furthermore, one study (24) was divided into 2 cohorts to reflect 2 different intervention contexts (e.g. hospital-based compared with home-based).

Study descriptions

Of the studies included in this systematic review, 7 were RCTs, 4 were controlled trials, 7 were longitudinal studies, with the remaining 3 either cross-sectional, case-crossover or case-control design. Study duration ranged from 5 to 32 weeks, with sample size ranging from 5 to 68 participants with post-polio conditions. Of the included studies, 5 focused on aerobic fitness interventions (4, 24–27), 7 on mixed interventions (aerobic fitness and muscular strengthening/functional activities) (3, 9, 28–32) and 9 on muscular strengthening interventions (22, 23, 33–39). Table II summarizes the study population, sample size, study design, follow-up time, type of exercise intervention, outcome measures and statistical analysis and associations.

Meta-analyses: the effect of exercise interventions

Fig. 2 shows the separate and combined effects of exercise interventions on the body function domain. When collated in this manner, aerobic, mixed and strengthening interventions were shown to have a

small-to-moderate effect (g ranging from 0.217 to 0.506; all p < 0.01); however, heterogeneity ranged from substantial to considerable (all p < 0.01; I² ranging from 70% to 83%). The overall effect on the body function domain indicated exercise interventions have a small positive effect (g=0.298; 95% CI=0.191– 0.406; p < 0.01); however, substantial to considerable heterogeneity was evident ($Q_{(22)} = 106.499$; p < 0.01; $I^2=79\%$). To determine the robustness of these findings, a leave-one-out sensitivity analysis was completed and the output reported in Table SV(A-D)¹. Table SVI¹ (A shows a sensitivity analysis where both (9, 22) were removed from the analysis, as participants used in these studies may have been repeated. For the combined body function domain, the results of this analysis were comparable to the main analysis, where all interventions and the combined overall effect were significant (all $p \le 0.01$) and the same effect size ranges were maintained (g ranging from 0.237 to 0.506). All data were substantial to considerably heterogeneous (all $p \le 0.01$; I² ranging from 73% to 83%).

Table III shows the meta-analysis summaries for each of the examined components and/or domains of the ICF. Within the body function domain, when all interventions were combined, small-to-moderate effects were identified in the lower limb, non-lower limb, and mental and sensory components (g ranging from 0.178 to 0.463; all p<0.01). Only the cardiovascular component was not significant (g=0.114; 95% CI=-0.034 to 0.262; p=0.13).

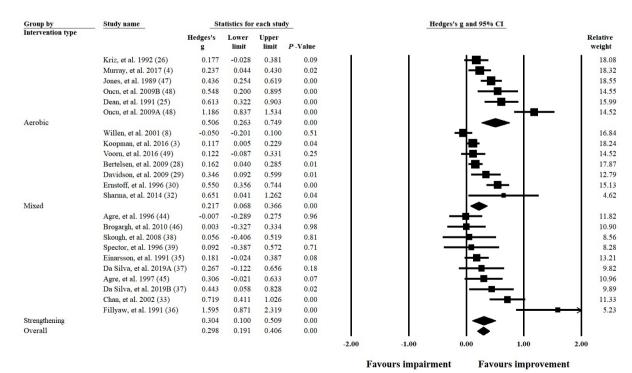


Fig. 2. Forest plot of the combined body function domains of the International Classification of Functioning, Disability and Health (ICF) disability framework. Studies are divided into their respective intervention types (aerobic fitness, mixed, and strengthening exercise).

 $\textbf{Table II.} \ \texttt{Experimental study designs according to study design and intervention type (cardiovascular fitness, mixed intervention methods and muscle strengthening)}$

Author	Study population	Diagnosis criteria used	Inclusion criteria	Study design	Intervention type and duration	Type of exercise intervention	Outcome measures	Statistical analysis	Effects of intervention
Agre et al. 1996 (44)	12 participants (7 F and 5 M), 35–60 years	Halstead and Rossi (1985)	Excluded those with <3+/5 on manual strength testing	Longitudinal	Muscle strengthening activities (12 weeks)	Muscle strength: 4 days a week, cuffed ankle weights (~ 1 to 1.5kg = 13-14 RPE). Leg extension, hold 5 seconds. 1 rep every 30 secs, 6 reps at first then up to RPE 17/20 or 10 reps	Exercise compliance. Neuromuscular: Ankle weight lifed (kg), Isometric quads: peak torque, endurance holding time (sec), MVC (Nm) Tension time index (Nms) Isokinetic quads: quads peak torque (Nm), hamstrings peak torque (Nm), hamstrings total work (Nm). EMG: Blocking (%), Jitter (usec), Macro EMG amplitude (mV). Serum CK	Wilcoxon matched pairs test. Friedman repeated measures ANOVA. Results in mean (SD), $p < 0.05$	
	7 participants (gender not reported), 35–65 years		Excluded those with <3+/5 on manual strength testing; allowed recent strength loss in 6 of 7 participants	Longitudinal	Muscle strengthening activities (12 weeks)	Muscle strength: 4 days a week ankle weights (~1 to 1.5kg = 13–14 RPE). Isokinetic (Tues/Fri): Leg extension, hold 5 seconds. 3x12 reps rest 1 min. Isometric (Mon/Thurs): 3x4 reps max. contractions 5 secs, rest 10 secs, 1 min between sets. Knee at 60 degrees from full extension	Exercise compliance. Neuromuscular: Ankle weight lifted (kg), Isometric quads: peak torque, endurance holding time (sec), tension time index (Nms), Isokinetic quads: quads total work (Nm), hamstrings peak torque (Nm), hamstrings total work (Nm). EMG: Fiber density, Blocking (%), Jitter (usec), Macro EMG amplitude (mV). Serum CK	Wilcoxon matched pairs test. Friedman repeated measures ANOVA, with Holm's post hoc comparisons. Results in mean (SD), p < 0.05	between strength training and quad isometric (p < 0.05) and
Bertelsen et al. 2009 (28)	50 participants (30 F and 20 M), age range 24–82 years, 4 dropped out due to illness within the follow up period.		Allowed new problems related to PPS; 74% had reported recent strength decrease	(prospective uncontrolled intervention	Mixed: Aerobic fitness, muscle strengthening and functional exercises. (3 and 15 months)	Individualised physiotherapy-based approach. Physiotherapy and subsequent exercise programme including both muscle strength and aerobic fitness interventions. Consisting of a combination of exercise (included in 80% of programmes), massage (78%), stretching (72%), home training (72%), walking (25%), and/or balance training (24%)	6MWT and timed-stands test	SF-36 and MF0-20 were converted into scales of 0 to 100. Non-parametric matched-pairs significance tests (Wilcoxon matched pair test)	Significantly improved 6MWT performance (BL: 378 m (SD 131), 3 months: 418 m (SD 122), 15 months: 418 m (SD 122), 15 months: 419 m (SD 138); both ρ <0.001 to BL) and timed-stands test performance (BL: 31 sec (SD 7), 3 months: 27 sec (SD 7), 15 months: 28 sec (SD 8); both ρ <0.001 to BL)
Brogardh et al. 2010 (46)	5 participants (3 M and 2 F), aged 64 years (SD 6.7), age range 55-71 years with late stages of polio	Halstead and Rossi (1985)	Excluded clinically unstable symptoms; Subjects had either Post-Polio Class III clinically stable or Class IV clinically unstable polio	Case- controlled pilot study	Muscle strengthening activities (5 weeks)	Muscle strength: 2x30 min weekly sessions of WBV - standing knees flexed at 40-55°. Repetition duration and number was 40 sec and 4 reps (start of intervention) and increased to 60 sec and 10 reps	knee extensor and flexor strength - MVC (Nm) in less and more affected limbs. Gait performance - TUG, Comfortable and	Mean relative difference = (diff pre to post/pretreatment x 100). Paired <i>t</i> -tests, $p < 0.05$	Strength: Isokinetic KEXT (less affected limb: 125 (SD 43) to 123 Nm (SD 46), more affected limb: 54 (SD 35) to 56 Nm (SD 39), isokinetic KFLX (less affected limb: 64 (SD 32) to 66 Nm (37), more affected limb: 26 (SD 21) to 24 Nm (SD 20), Gait performance: TUG (11.0 (SD 2.0) to 10.9 sec (SD 1.9), comfortable gait speed (10.2 (SD 2.6) to 9.4 sec (SD 1.1), fast gait speed (7.2 (SD 1.9) to 7.1 sec (SD 1.7), and 6MWT (422 (SD 10.5) to 7.1 sec (SD 1.7), and 6MWT (422 (SD 10.5) to 9.4 TM (MS 92)
Chan et al. 2003 (33)	10 post-polio patients (9 F and 1 M): 5 in training group (4 F and 1 M), 5 in control group (5F)	Post-polio diagnosis, affecting one or both upper limbs, moderate motor neuronal loss in median-innervated thenar muscles with MUNE 10–90	Excluded those with MUNE <10, as increase in strength unlikely	RCT	Muscular strengthening activities (12 weeks)	3x8 upper limb isometric contractions (50–70% MVC), 5 min rest between sets. 3xweekly for 12 weeks	Thenar MVC, voluntary activation, estimated motor unit number, and surface detected motor unit action potential	One-way ANOVA. Post hoc analysis using Scheffe test. Training changes analysed using paired t-tests, between groups compared with independent t-tests	Improved thenar MVC force production and level of voluntary

	Study	Diagnosis	Inclusion	Study	Intervention type and	Type of exercise			
Author	Study population	Diagnosis criteria used	criteria	Study design	duration	Type of exercise intervention	Outcome measures	Statistical analysis	Effects of intervention
Da Silva et al. 2019 (37)		National Institute of Health, 2015. PPS diagnosis not required but most participants had it; various criteria may have been used	Excluded those unable to tolerate weight bearing for 20 min	Random order, Crossover Exploratory Experimental Intervention	of 8 sessions -	Two intervention groups with one group participating in low intensity WBV 4-week block of 8 sessions first (group Lo-Hi), and higher intensity WBV 4-week block of 8 sessions second	10mWT, 2mWT, BPI Interference, Severity, PSQI, FSS	Descriptive statistics, Mann-Whitney U tests for between subject changes, Non- parametric Wilcoxon for within subject changes, Friedman's analysis of variance	
Davidson et al. 2009 (29)	27 post-polio patients (17 M and 10 F), mean age of 56.4 years, age range 44–74 years	Informal PPS criteria; definite history of polio and new physical disability and symptoms typical of PPS	Allowed those with new physical disability and symptoms typical of PPS	Longitudinal	muscle strengthening and aerobic	An initial 3 per week for 3 weeks of a supervised exercise programme including a timed interval training circuit (based on CV fitness), stretching, hydrotherapy, relaxation techniques. Self-directed exercise until follow up	Muscle strength (sit to stand, grip strength of dominant hand), muscle endurance (10m shuttle walk test). Hospital anxiety and depression scale, Illness perception questionnaire	Non-parametric matched-pairs significance tests (Wilcoxon), Spearman rank correlations. Mann-Whitney test	Positive: Circuit training and shuttle test 29%), RPE, STS (20%)
	48 post-polio participants (38 F and 10 M, age ranging from 32 to 71	PPS criteria; confirmed history of		Cross- sectional study	Aerobic fitness activities (6 weeks)	Two-min walking at 1.6 km/hr followed by an increase of 0.8 km/hr each min till a comfortable cadence was reached	Movement economy and cardio-respiratory conditioning based on movement economy index (MEI) and cardiorespiratory conditioning index (CRCI) based, maximum heart rate and VO ₂	2x2 ANOVA, Pearson product moment correlations and <i>t</i> -tests, $p < 0.05$	MEIs were significantly different between the normal and reduced movement economy groups based on the manner in which the groups were categorised (ρ < 0.01). MEIs were not different for the conditioned groups (ρ > 0.05). CRCIs were significantly different between the normal and reduced conditioning groups (ρ > 0.05). CRCIs were significantly different between the normal and reduced conditioning groups based on the manner in which the groups were categorised (ρ < 0.01). CRCIs were not significantly different for the groups with normal and reduced movement economy (ρ > 0.05)
Einarsson 1991 (35)	155 participants	Informal PPS criteria	Excluded those with <3+/5 on manual strength testing	Longitudinal study	Muscular strengthening activities (6 to 12 months post training)	3 sessions/week of 12 sets of 8 isokinetic contractions, each at 180"/sec angular speed interposed with 12 sets of isolated 4-second isometric contractions at 30°, 60°		Non parametric Wilcoxon test, Spearman rank correlation test was used for analysis of correlation	Significant (p < 0.01) increase (mean 29%) in insometric knee-extension muscle strength measured at 60° knee angle and in isokinetic knee-extension strength (mean 24%), measured as peak torques at angular velocities of 30°, 60°, 180° and 300° per second
Ernstoff et al. 1996 (30)	12 (9 F and 3 M). Aged 39 to 50 (mean 42 years), 5 lost to follow up. All but 4 had symptoms according to Halstead's criteria	Halstead (1987)	Excluded those unable to perform full knee extension or had severe weakness; those with <3/5 on quad manual strength testing		Mixed: both muscle strengthening and aerobic fitness activities (22 weeks)	2xweek for 22 weeks. Group and home programmes. 60 min with 5 min warm up, low resistance, high rep ex for upper/lower/trunk. 5 mins cycling at 60–80% GXT		Wilcoxon's signed rank test for statistical analysis. Spearman's rank correlation	Positive: 1) Less fatigue (reduction in peak torque) in weaker leg after training. 2) significant increases in strength of right elbow ext. Right wrist ext., hip abd laterally. 3) significant reduct in HR (133 vs 127 after), showing fitness
Fillyaw et al. 1991 (36)	17 (6 lost to follow-up excluded from analysis) Halstead and Rossi criteria for post-polio, MMT fair +, both quads Age 51.3 (SD 12.3)	Halstead and Rossi (1985)	Excluded those with less than fair quads; <3/5 on manual strength testing	Controlled trial, randomised by muscle group (quads vs biceps)	Muscular strengthening activities (2 years)	14 exercised quads muscle, 3 biceps. 10RM through knee ext. or elbow flex. without pain/fatigue. HEP based off 10RM 3×10 reps every other day. Set 1: 50% 10RM, 2: 75% 10RM, 3: 100% 10 RM. 5 mins. rest between	Maximum isometric torque (MIT), endurance integral (EI). 10 RM every 2 weeks	Analysis of variance between exercise and control group for MIT and EI using SAS General Linear Model	Positive: 1) Exercise and strength (10RM, mean increase 78%, $p < 0,001$). 2) Exercise and MIT: 8.4%, $p = 0.04$. 3) Schange in exercise and EI
Jones et al. 1989 (47)	45 patients (37 completed the study) (age between 30 and 60 years)	Informal PPS criteria; hospital records	Adequate strength in at least one lower extremity to pedal an 'exercycle' and 'arm cycle ergometer'	RCT	Aerobic fitness activities (16 weeks)	The training group trained at 70–75% of the heart rate plus resting heart rate on ergometer. 15–20 min exercise/session	per min, maximal heart	Mean (SD) scores for pre and post treatment differences, multivariate analysis of variance was used to compare changes, Hotelling's T2 for statistical test	Improvement in watts attained during testing, duration of testing, and VO ₂ max. Positive impact of cardiorespiratory training on exercise group

Table II	• Cont.								
Author	Study population	Diagnosis criteria used	Inclusion criteria	Study design	Intervention type and duration	Type of exercise intervention	Outcome measures	Statistical analysis	Effects of intervention
Koopman et al. 2016 (3)	68 participants (age between 18 and 75)	March of Dimes (2000)		multicentre single	Mixed: aerobic fitness, muscle strengthening and functional exercises. (>6 months)	Exercise Therapy: 3 sessions/week aerobic exercise on a cycle ergometer. Intensity increased from 60% to 70% heart rate reserve. Duration increased from 28 to 38 min	Submaximal heart rate during exercise, muscle strength (maximal isokinetic voluntary torque of quadriceps muscles), functional capacity (Timed-Up-and-Go test and 2-Min Walk test), and actual daily physical activity level	Primary analysis for efficacy: linear mixed models, with group and pre-treatment score of the outcome as covariates (primary analyses)	No beneficial effect of ET on fatigue, activities or HRQoL compared with UC in patients with PPS
Kriz et al. 1992 (26)	29 subjects at baseline, 20 at follow up	Informal PPS criteria	Physician screening; participants had to have adequate trunk and upper extremity strength for ergometry	RCT	Aerobic fitness activities (16 weeks)	Upper extremity aerobic exercise programme. 3xper week for 20 min. Intensity at 70–75% HRR plus RHR	HRrest, HRmax, BP at rest, BP immediately post exercise, VO ₂ max, RER, VEmax, RR	Change scores were compared using MANOVA. Univariate F-test was used to determine $p < 0.05$	Positive: Exercise programme and fitness (VEMax – 17%, V VCOZ – 20%, VO ₂ Max – 19% 12% - Power, exercise time - 10%)
Murray et al. 2017 (4)	55 subjects	Informal PPS criteria	Excluded those with severe weakness; those with unstable muscle groups per ACSM; severe fatigue or recent onset of weakness	single blinded - RCT	Aerobic fitness activities (8 weeks)	Home-based arm ergometry at an intensity of 50%–70% maximum heart rate, compared with usual physiotherapy care	The 6-MAT, Fatigue Severity Scale, Physical Activity Scale for Individuals with Physical Disabilities SF-36	Sample t-test for intergroup comparison and paired t-test for within group comparison. Linear regression modelling or Poisson regression. A significance level of p < 0.05 was set	No significant association between exercise and 6-MAT or 6MWT
Oncu et al. 2009 (48)		Halstead (1991)	Allowed those with new lower limb weakness. Allowed those with ambulatory ability of 30 m in 60 sec	RCT	Aerobic fitness and stretching activities (8 weeks)	3 session/week of 1.5 hours. Flexibility training, aerobic fitness on treadmill involving walking for 30 min with 3 rest periods at an intensity of 50–70% of pVO ₃ and at a level of 13–15 on the Borg Scale. Patients in group 2 performed flexibility and aerobic exercises. A walking programme was undertaken by the patients in group 2 as an aerobic exercise at 50–70% of pVO,	(pVO ₂) and carbon dioxide production (VCO ₂)	Mann—Whitney U test for numeric data, Fisher's exact or chi-square tests for nominal data, non-parametric Wilcoxon test, Mann—Whitney U test for pre- vs post-exercise differences	Improvement was observed in the parameters of fatigue and quality of life in both the hospital exercise group and the home exercise group. An increase in functiona capacity was also found in the hospital exercise group
Sharma et al. 2014 (32)	21 participants (13 F and 8 M) age between 18 and 65	Halstead (1985)	Allowed body position change to reduce/ eliminate gravity for weaker muscle groups	Controlled trial	Aerobic fitness activities (4 weeks)	Group A: Performed exercise and lifestyle modification. Exercises were divided into 4 phases. Phase 1: warm up, gentle AROM; Phase 2: strengthening exercises, 8 muscle groups; Phase 3: aerobic exercise, 10 mins static cycling, moderate intensity (i.e. RPE of 13–15 on modified Borg's scale) Phase 4: Cool down, gentle PROM (5 reps)		Wilcoxon signed-rank test for within-group differences in FSS score, Kruskal-Wallis test for between groups differences, Mean difference, Mean difference in ZMWD within each group using paired t-test	difference within group A and group
Skough et al. 2008 (38)	14 subjects at baseline and follow up (8 F and 6 M)	March of Dimes (2000)	Allowed those who were able to walk with or without a walking aid for 6 min	Randomized, placebo- controlled pilot study	Muscular strengthening activities (12 weeks)	Resistance training at 10–11 on the Borg Rate of Perceived Exertion scale for 30 min/session. the initial work-load was 50–60% of 1 repetition maximum (1RM) and was successively increased to an intensity of 70–80% of 1RM	Sit stand sit, timed up & go, 6-min walk, muscle strength measurement by means of dynamic dynamometer and short-form (SF)-36 questionnaire	Wilcox on signed- rank test was used to analyse differences within groups and Mann-Whitney U test for differences between groups. A $p < 0.05$ was taken as statistically significant	Positive: Significant associations between exercise programme and STS, 6MWT and muscle strength
Spector et al. 1996 (39)	6 subjects at baseline and follow up		Excluded those with <3+/5 on manual strength testing; allowed limbs described ranging from asymptomatic to flaccid	Controlled study	Muscle strengthening, 10 weeks 4 to 6 weeks post training 5 months	Progressive resistance exercise of knee and elbow extensors representing both symptomatic and asymptomatic muscles	Fatigue Severity Scale, isometric and dynamic strength, MRI. Biopsies	t-tests	Positive: PRT and dynamic strength (3RM), 10 week and 5 months

Table II	. Cont.								
Author	Study population	Diagnosis criteria used	Inclusion criteria	Study design	Intervention type and duration	Type of exercise intervention	Outcome measures	Statistical analysis	Effects of intervention
Voorn et al. 2016 (49)	44 participants (24 F and 20 M)	March of Dimes (2000)	Allowed those able to walk at least around their house	RCT	Mixed: aerobic fitness, muscle strengthening and functional exercises (3xweek, 4 months)	Home-based aerobic training programme on a bicycle ergometer 3xweekly and a supervised group training 1xweek (muscle strengthening functional exercise)	Muscle endurance, Muscle strength (MVT). Resting HR, oxygen consumption at the AT, VO ₂ submax, RER submax, and RPE submax	test and Mann-Whitney	Training programme did not significantly improve muscle function nor CV fitness
Willen et al. 2001 (8)	30 participants at baseline, 28 at follow up	Informal PPS criteria; late effects of polio	Excluded National Rehabilitation Post-Polio Limb Classification of I (no history of remote or recent weakness)	Controlled trial: Before- after tests	Mixed (Aerobic fitness, muscle strengthening and functional exercises) average of 5 months	40 min of general fitness training session in warm water twice weekly	Peak load, Peak oxygen uptake, Peak HR, Berg balance scale, Visual analogue scale, Pain scale, Physical activity scale for the Elderly, and NHP.	Wilcoxon's signed- rank test and the Mann-Whitney U test A significance level of $p = 0.05$ was used throughout the study	Positive: exercise and function (lower HR and self-reported improvement in physical fitness)

AROM: Active Range of Motion; BL: baseline; BPI: Brief Pain Inventory; CBT: Cognitive behavioural therapy; CK- Creatine Kinase; CRCI: Cardiorespiratory conditioning index; CSA: Cross-sectional area; CV: Cardiovascular; EI: Endurance integral; EMG: Electromyography; ET: Exercise therapy; Ext: Extension; F: female; FIS: Fatigue Impact Scale; Flex: Flexion; FSS: Fatigue severity scale; GLM: General linear model; GXT: Graded Exercise Test; HEP: Home exercise programme; HR: Heart rate; HRQoL: Health related quality of life; KEXT: knee extensor, KFLX: knee flexor; Kg: Kilogram; L: Litre; M: male; MAT- Min arm test; Max: Maximum; MEI: Movement economy index; MFI: Multidimensional fatigue inventory; MIT: Maximum isometric torque; mL: Millilitre; MRI: Magnetic Resonance Imaging; MUNE: Motor Unit Number Estimate; MVC: Maximal voluntary contraction; mV: millivolt; MVT: Muscle strength; MWT: Min Walk Test; Nm: Newton metre; NS: Not stated; NHP: Nottingham health profile; pVO₂: Maximum oxygen consumption; PHQ: Patient health questionnaire; PPS: Post-polio syndrome; PROM: Passive Range of Motion; PROMIS: Patient reported outcome measurement information system; PSQI: Pittsburgh sleep quality index; RCT; Randomised controlled trial; RER: respiratory exchange ratio; RHR: Resting heart rate; RM: Repetition max; RPE: Rate of perceived exertion; SD: Standard deviation; Sec: Seconds; SF: short-form; SIP-68: Sickness Impact Profile; STS: Sit-to-stand; TUG: Timed up and go; usec: microsecond; UC: Usual care; VO₃: Oxygen consumption; WBV: Whole body vibration.

Significant heterogeneity was present for each of the components within the body function domain and ranged from moderate to considerable (all $p \le 0.01$; I² ranging from 54% to 78%). Output from the leave-one-out sensitivity analysis is shown in Table SV(E, H, I and L)¹.

Table III. Meta-analysis output for each of the components examined in the International Classification of Functioning, Disability and Health. Positive direction denotes the respective intervention mode having a beneficial effect on the respective domain and/or component.

ICF domain				
(component)	Intervention	Hedges g	95% CI	<i>p</i> -value
Body function				
(lower limb)	Aerobic $(n=1)$	0.585	-0.036 to 1.205	0.06
	Mixed $(n=5)$	0.140	0.002 to 0.277	0.05
	Muscle strengthening $(n=7)$	0.232	-0.004 to 0.468	0.05*
	Overall $(n=13)$	0.178	0.061 to 0.294	< 0.01*
Body function	Aerobic $(n=2)$	0.260	0.070 to 0.451	0.01
(non-lower limb)	Mixed $(n=1)$	0.837	0.585 to 1.089	< 0.01
	Muscle strengthening $(n=2)$	0.337	-0.341 to 1.015	0.33*
	Overall $(n=5)$	0.463	0.315 to 0.611	< 0.01*
Body function	Aerobic $(n=5)$	0.373	0.100 to 0.646	0.01
(cardiovascular)	Mixed $(n=3)$	0.007	-0.169 to 0.183	0.94*
	Overall $(n=8)$	0.114	-0.034 to 0.262	0.13*
Body function	Aerobic $(n=4)$	0.733	0.146 to 1.175	< 0.01*
(mental and	Mixed $(n=4)$	0.197	0.080 to 0.314	< 0.01
sensory)	Muscle strengthening $(n=2)$	0.356	0.083 to 0.630	0.01
	Overall $(n=10)$	0.250	0.146 to 0.355	< 0.01*
Activity and	Aerobic $(n=1)$	0.173	-0.024 to 0.371	0.09
participation	Mixed $(n=5)$	0.145	0.086 to 0.204	< 0.01
	Muscle strengthening $(n=4)$	0.071	-0.153 to 0.296	0.53
	Overall $(n=10)$	0.143	0.088 to 0.198	< 0.01

^{*}Denotes findings with significant and moderate to substantial heterogeneity. CI is confidence interval, ICF is International Classification of Functioning, Disability and Health, and n is the number of studies used in the respective analysis.

Aerobic interventions within the body function domain were shown to produce significant small-to-large effects in the non-lower limb, cardiovascular, and mental and sensory components (g ranging from 0.260 to 0.733; all $p \le 0.01$). Data were homogenous for the finding in the non-lower limb (Q(1)=0.151; p=0.70; I^2 =0%), while substantial heterogeneity was found within the cardiovascular and mental and sensory components (both p=0.01; $I^2 \ge 68$ %). The effect of aerobic interventions on the lower limb component was not explored, due to an insufficient number of studies (n=1). Output from the leave-one-out sensitivity analysis is shown in Table SV(J and M) 1 .

For mixed interventions within the body function domain, small improvements were found for the lower limb and mental and sensory components (g=0.140and 0.197 respectively; both $p \le 0.05$), while the cardiovascular component was not significant (g=0.007; 95% CI=-0.169 to 0.183; p=0.94). Data for mixed interventions were not interpreted for the non-lower limb component due to an insufficient number of studies (n=1). For each of these findings, heterogeneity was not significant (all $p \ge 0.20$; $I^2 \le 35\%$). Output from the leave-one-out sensitivity analysis is shown in Table SV(F and N)¹. Removal of (9) resulted in significance being lost for mixed interventions in the lower limb component (g = 0.127; 95% CI = -0.028 to 0.281; p=0.11), while there were insufficient study numbers to interpret the cardiovascular component (g=-0.092; 95% CI=-0.299 to 0.115; p=0.38), shown in Table SVI¹.

For strengthening interventions, a positive small-tomoderate effect was found for the lower limb and mental and sensory components (g=0.232 and 0.356 respectively; both $p \le 0.05$). Although substantial heterogeneity was present for the lower limb ($Q_{(6)} = 18.614$; p < 0.01; I²=68%), data were considered homogenous for the mental and sensory component ($Q_{(1)}=0.398$; p=0.53; $I^2=0\%$). The main effect here appears to be between muscle strengthening exercise and fatigue, as fatigue measures accounted for 36% (13 of 36) compared with pain measures (19%) of the mental and sensory measures reported in the included studies. Within the non-lower limb component, muscle strengthening did not produce a significant effect (g=0.337; 95% CI=-0.341 to 1.015; p=0.33), but substantial to considerable heterogeneity was also present $(Q_{(1)} = 5.379; p = 0.02; I^2 = 81\%)$. Output from the leave-one-out sensitivity analysis is shown in Table SV(G and K)¹. Removal of (22) resulted in a loss of significance for muscle strengthening in the lower limb component (g=0.235; 95% CI=-0.049 to 0.519; p=0.10; Table SVI (B)¹), and data were substantially heterogeneous ($Q_{(5)} = 17.887$; p < 0.01; $I^2 = 72\%$). This study did not contribute to the remaining components.

For the combined activity and participation domain, exercise interventions produced a small positive effect (g=0.143; 95% CI=0.088-0.198; p<0.01). A small

positive effect was also found for mixed interventions (g=0.145; 95% CI=0.086-0.204; p<0.01). The aerobic and strengthening interventions were not significant $(g=0.173 \text{ and } 0.071 \text{ respectively}; \text{ both } p\geq0.09)$. All data sets in this domain were homogenous (all $p\geq0.73$; $I^2=0\%$). Output from the leave-one-out sensitivity analysis is shown in Table SV(O-Q)¹.

Meta-regression

Meta-regression was performed on the effect size estimates from the combined body function domain and the duration of the exercise intervention (Fig. 3). The overall test of the model was not significant ($Q_{(1)} = 1.06$; coefficient = -0.008; 95% CI -0.024 to 0.008; p = 0.30). In addition, the goodness of fit for this outcome was deemed significant ($Q_{(20)} = 87.810$; p < 0.01), suggesting the dispersion of effects is outside the range expected from standard error alone. The analysis was conducted without (36), as the intervention duration by these authors far exceeded that of any other study and we believed it to be an outlier. Similar results were found for the activity and participation domain $(Q_{(1)}=0.410; coefficient=-0.002; 95\% CI=-0.008 to$ 0.004; p=0.52; Fig. 4). However, goodness of fit was not significant $(Q_{(8)} = 2.310; p = 0.97)$.

Regression of Hedges's g on Intervention duration

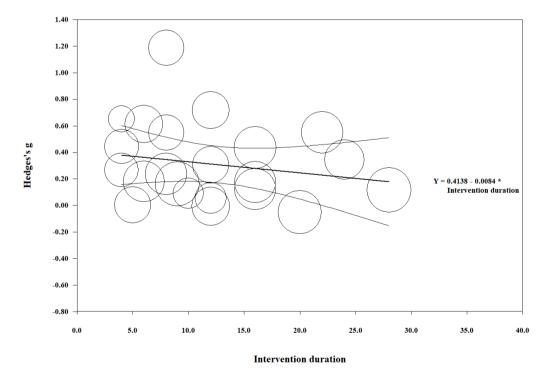


Fig. 3. Meta-regression analysis of intervention duration (weeks) and the effect size (g) for outcomes within the body function component of the International Classification of Functioning, Disability and Health (ICF) disability framework. Each study (n=22) is depicted by a circle, with the circle size representing the relative weight attributed to each effect size. Note that (36) was removed from the analysis due to the long duration of the intervention.

Regression of Hedges's g on Intervention duration

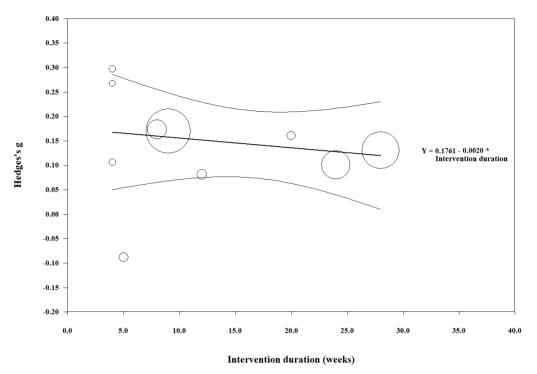


Fig. 4. Meta-regression analysis of intervention duration (weeks) and the effect size (g) for outcomes within the combined activity and participation components of the International Classification of Functioning, Disability and Health (ICF) disability framework. Each study (n=10) is depicted by a circle, with the circle size representing the relative weight attributed to each effect size.

Publication bias

Possible publication bias was examined on the combined body function domain, each of the individual components, and the combined participation and activity domain. The funnel plot for the collated body

function domain is shown in Fig. 5, where significant publication bias was identified using both the Begg and Mazumdar rank correlation test (Kendall's τ =0.299; p=0.03 (1-tailed)) and Eggers linear regression method (intercept=2.840; p=0.01 (2-tailed)). Application of Duval and Tweedie's trim and fill method indicated



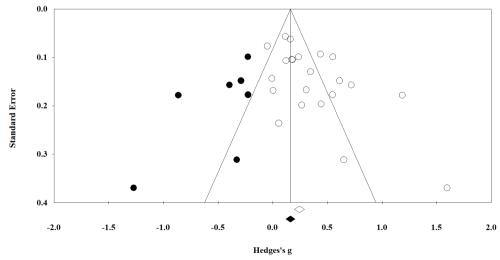


Fig. 5. Funnel plot of the combined body function domain. The included and imputed studies are denoted by the white and black circles, respectively. Studies reported to the right of 0 represent exercise interventions having a positive effect on the respective domain and/or component.

Funnel Plot of Standard Error by Hedges's g

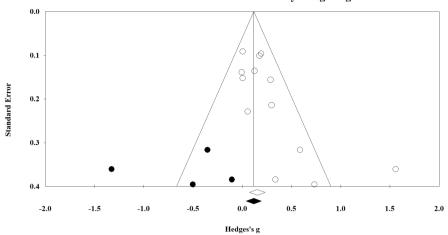


Fig. 6. Funnel plot of the lower-limb component of the body function domain. The included and imputed studies are denoted by the white and black circles, respectively. Studies reported to the right of 0 represent exercise interventions having a positive effect on the respective domain and/or component.

that 7 studies were missing to the left of the analysis (negative; implying that exercise interventions may impair outcomes within the body function component). These studies ranged from g = -0.233 to -1.276.

As outlined in Table III, there is limited evidence to suggest that exercise interventions are likely to have a debilitating effect on function (particularly up to the range shown statistically here). We consider it unlikely that such stark findings would have gone unpublished and, thus, have chosen to ignore this correction. However, even if the correction were accepted, a small beneficial effect on the body function domain still results (g=0.175; 95% CI 0.046–0.303). Fig. 6 shows the funnel plot for the lower limb component of the body function domain, which also indicated significant publication bias (Kendall's τ =0.487; intercept=2.100; both $p \le 0.02$). The analysis suggested that 4 studies were missing that imply exercise has a small-to-large negative effect on this component (g ranging from -0.113 to -1.333). Dissimilar to the commentary provided above on the combined body function domain, the correction results in the finding becoming non-significant (g=0.120; 95% CI=-0.037-0.277). However, as stated above, we believe it is unlikely that studies with such prominent contrary findings to the present analysis would not have been published and thus, have chosen to ignore the corrected data. Publication bias was not evident for each of the remaining components of body function or in the combined activity and participation domain (all Kendall's $\tau \le 0.327$; intercept ≤ 2.839 ; all $p \ge 0.08$).

DISCUSSION

This systematic review summarizes the role of exercise for muscular strength and cardiovascular fitness in polio survivors. The 21 studies were grouped into

respective ICF domains and/or components based on the ICF codes (40) and administered to quantitative synthesis. The overall results for the body function component (motor function, cardiovascular, mental and sensory domains) show that interventions have an effect favouring improvement in the body function of polio survivors. Results indicating improvement were also found for measures of activity and participation related to exercise. These findings provide clarification for a 2008 meta-analysis, which questioned the inclusion of muscular strengthening interventions in research (10), and build on the conclusions of the 2010 and 2011 reviews that stated that rehabilitation interventions seemed effective (14, 41).

Study heterogeneity and quality

Heterogeneity varied among the findings of this study. Although some findings were homogeneous (the combined activity and participation components), most findings displayed moderate to substantial heterogeneity, which remained following sensitivity analyses. This may be explained by when this set of studies was published (all since 2001), in relation to the emergence of the ICF framework (2001), which oriented researchers to human functioning, resulting in more frequent inclusion of activity and participation measures. These studies were also of a higher quality: scoring 71+% (Table SIV¹) except for one (31) (at 59%). In addition, we observed a difference in quality (based on our assessment using a reduced Downs and Black checklist (15), when comparing studies published before and after 2001. Studies in this review published since 2001 appeared to be of higher quality, when assessed using this quality appraisal checklist.

International Classification of Functioning, Disability and Health

The results were presented in ICF components and domains, to enable meaningful interpretations to be made in a familiar framework of disability. The body function component is split into domains of motor function, cardiovascular fitness, and mental and sensory, enabling the key topics of this review to be discerned. The activity and participation components' domains are combined, as each is oriented to the performance of tasks. Combining these latter 2 domains can provide context for potential positive outcomes and prognosis for social independence (40). The Core Set for PPS proposed by Bocker et al. (2016) helped to narrow the ICF categories, providing clearer directions for assessment and documentation in clinical practice and research (17). This was an overall strength of this review outlining the effectiveness of muscular strengthening and aerobic fitness activities across a range of domains (e.g. body function – cardiovascular d450: walking), while still allowing specificity to individual outcome items (e.g. 6-min walk test as measure of fitness).

Intervention duration

Studies ranged in duration from 5 to 32 weeks. The meta-regression analyses of intervention durations vs effect (Figs 3 and 4) excluded the 2-year study (36), which was an outlier that skewed the regression line. This study (36) showed the strongest effect size amongst the studies, suggesting continued gains in the long term could be established in focal muscle groups when a non-fatiguing protocol is established in-clinic and continued as a home programme. Particularly able, motivated, and resourced polio survivors may have been recruited in this study, possibly lowering the attrition risk and biasing the outcomes. Current evidence seems to suggest progression of symptoms may not be as rapid as anticipated (8); however, without further long-term studies, it is difficult to confirm the rate of deterioration or the maintenance of key gains in the active population.

The body function domain analysis shows the dominant cluster within the remaining studies being between 4 and 16 weeks of intervention, this is reflective of interventional exercise studies, which look for measurable effects within several months. A similar analysis for activity and participation domains (Fig. 4) shows a weak overall regression line. Both sets of domains had an apparent negative (waning) effect slope in response to duration. A subtle gradual worsening of symptoms amongst participants may explain this effect slope, or the protocols may not have managed fatigue adequately. Polio survivors can be affected by fatigue within and between sessions, and serially. We recommend exercise protocols that acknowledge and

limit fatigue, concurrent with education on fatigue management, with the aim of improving long-term motivation and adherence to exercise.

Effect sizes

Small-to-moderate improvement effects due to exercise interventions were seen in the motor function components and mental and sensory domain, while effects that appeared to be of clinical interest were identified in the cardiovascular component (not significant) and activity and participation domains, as outlined in Table III.

Although the effect sizes were modest, clinicians and polio survivors should derive confidence from further evidence of exercise favouring improvement across a range of contexts. What might be most reassuring, is that the strongest exercise effect was in outcomes within the mental and sensory domain (outcomes related to pain and fatigue) favouring improvement in 2 highly prevalent symptoms in post-polio conditions. This challenges the findings of an earlier systematic review and meta-analysis (10), identifying no associations between exercise and improved fatigue management, and may be due to the increased number of studies included in the current research.

Body function domains

Motor function component. A prominent component of polio sequelae is increasing weakness across muscle groups (4). Exercise can be perceived by polio survivors and clinicians as disadvantageous to maintaining function, due to discerning effects such as pain and fatigue. Long-term stress on polio-surviving motor units is widely accepted as precipitating muscle weakness through the degradation or loss of these motor units (10). Among the studies examined in the current analysis, strength outcomes in 5 studies (31, 33, 34, 38, 39) had limited effects on either improvement or impairment. This demonstrates the need for further high-quality mode-testing studies to discern intervention modes with potential adverse effects across LEoP and PPS populations.

In their 2016 article, Vroon et al (9) discuss nuances of strength and cardiovascular exercise prescription in this population: anaerobic threshold as a tolerance limit, musculature chronically utilised being adapted to higher loading, the limitations of non-whole body exercise, and individualization (14). We agree that these factors are significant contributors to the heterogeneity of results within studies on polio survivors, and need to be balanced against participation outcomes.

Exercise prescription criteria for polio survivors engaging in strengthening activities, such as those summarised by Gonzalez et al. in 2010 (14), should be utilised. Most studies in this analysis excluded candidates with severe weakness or excluded individuals' muscle groups

with a manual grade of less than 3/5. Further, studies highlight the importance of monitoring and responding to person-specific limits or adverse events during interventions with individualized modifications (5, 29). Without applying itemized criteria to set exercise participation limits, harmful or null overall exercise effects may arise in this population (5). It is essential that clinicians adhere to these tenants (prescription and exclusion) of exercise when treating polio survivors. The variety of measures and muscle groups strengthened effectively and safely across the included studies in this review indicates that strength exercise is suitable for polio survivors; a finding that is consistent with previous literature (10).

Cardiovascular component. The criteria of included studies allowed a broad range of assistive device use, limb bracing use, and fatigue profiles amongst participants. Exclusions usually reflected the physical requirements of the cardiovascular intervention mode and the severity of existing weakness. Barriers to polio survivors maintaining or improving cardiovascular fitness include: global and peripheral fatigue, muscle weakness profile, use of assistive devices, activity choices, and the risk of falls (29). Thus, an individual's profile determines the feasibility of fitness exercise mode.

Clinically, exercise mode decisions should be similarly based on polio survivors' ability and symptoms, accommodating any evident body limitations and assistive technology use (5). The studies incorporating cardiovascular domain interventions used combinations of limb use, body position and interface. This demonstrates polio survivors' tolerance of a variety of cardiovascular exercise modes already available in clinical settings.

Mental and sensory component. The results of this review indicated links between muscle strengthening exercise and mental and sensory component, particularly fatigue (36% of the mental and sensory measures reported in the included studies). Fatigue is multidimensional and complex, and the measures used in the included studies (FSS, FIS, MFI-20, VAS) are non-specific to body system or condition (32). Fatigue is a pervasive symptom amongst polio survivors and is more prevalent than weakness (5). We recommend that consistent use of the fatigue measures should be used with polio survivors in research and clinical settings, and strict muscle pain and fatigue avoidance protocols should be adopted as demonstrated, consistent with previous protocols outlined in the literature (36, 42). In contrast, pain measures accounted for 19% of the mental and sensory measures reported, a representation much lower than expected, as it is important to monitor pain during exercise so that symptoms of pain or soreness in the polio survivors involved are not excessive (2). The presence of only one mental and sensory weakness measure among the included studies may be explained by the abundance of objective motor function testing measures performed. The inclusion of subjective weakness as a mental and sensory evaluation measure could capture the lived experience of functional strength during activity and may add scope to studies of non-motor oriented post-polio conditions (43).

Limitations

This systematic review and meta-analysis addressed limitations across the literature regarding polio survivors exercising and previous meta-analyses, such as (10); there were a number of points of improvement. A key assumption of the analysis carried out was that independent studies were unique cohorts. This was not the case in 2 examples: subjects in (22) were recruited from the cohort of 12 subjects originally studied in (23). Similarly (9) followed the same cohort as (3). Furthermore, our systematic search of the literature only included studies available in English; hence, we recommend that future reviews include languages other than English within searches, particularly given contemporary translation options outlined in the Cochrane Handbook (19). It is possible that such studies could influence the publication bias highlighted in this review. Further research into more individualized approaches to exercise prescription for polio survivors would greatly advance research in this area.

CONCLUSION

The findings of this review and analysis provide "very low level evidence" (according to the Grading of Recommendations Assessment, Development and Evaluate; GRADE) to polio survivors, clinicians and researchers. The main findings of this review relate specifically to changes in body function, and activity and participation, and include evidence of effect on improved functioning without furthering debility in polio survivors. This systematic review and meta-analysis provides additional insights into effects associated with exercise, across various types of interventions, in polio survivors, and advances the level of methodological quality of research in this area. Although there was evidence demonstrating effect across domains, due to inherent biases within the literature to date, further and high-quality primary exercise-focused research is required in order to strengthen the certainty of evidence regarding important research questions about the ongoing health of polio survivors.

The authors have no conflict of interest to declare.

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Table SI. Draft search strategy performed in PubMed on 21 February 2020. Searches were performed in the article title, abstract, and keywords fields

Concept	Line number	Entry	Hits
PPS or LeOP	1	postpoliomyelitis	822
	2	late effects of polio	168
	3	post polio	1,260
	4	post-polio	594
	5	polio survivors	279
	6	late poliomyelitis	452
	7	post polio syndrome	969
	8	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	2,062
Exercise intervention	9	exercise therap*	40,875
	10	resistance training	22,528
	11	group exercis*	894
	12	exercise movement techniques	8,734
	13	therapeutic exercise	124,612
	14	physiotherapy*	47,916
	15	aquatic training	3,818
	16	water training	40,583
	17	sub-maximal aerobic training	53
	18	aerobic training	15,575
	19	low-intensity muscle strengthening	35
	20	muscle strengthen*	1,101
	21	muscle strength*	34,464
	22	yoga	5,351
	23	flexibility training	8,434
	24	rehabilitat*	425,895
	25	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24	634,174
Combined concepts	26	8 AND 25	579

Table SII. Checklist for measuring data quality

Criteria	Score
Reporting	
1. Is the hypothesis/aim/objective clearly described?	Y/N
2. Are the main outcomes to be measured clearly described in the Introduction and Methods section?	Y/N
3. Are the characteristics of the patients included in the study clearly described?	Y/N
4. Are the main findings of the study clearly described?	Y/N
5. Does the study provide estimates of random variability in the data for the main outcomes?	Y/N
6. Have the characteristics of patients lost to follow-up been described?	Y/N
7. Have the actual probability values been reported (e.g. 0.035 rather than<0.05) for the main outcomes except where the probability value is less than 0.001?	Y/N
External validity	
8. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	Y/N/UD
9. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	Y/N/UD
10. In cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	Y/N/UD
11. Were the statistical tests used to assess the main outcomes appropriate?	Y/N/UD
12. Were the main outcomes used accurate (valid and reliable)?	Y/N/UD
13. Were the assessments of exercise interventions assessed by valid and reliable measures?	Y/N/UD
Internal validity – confounding (selection bias)	
14. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same time period?	Y/N/UD
15. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	Y/N/UD
16. Were losses to follow-up taken into account?	Y/N/UD
Power	
17. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	Y/N/UD

Y: yes; N: no; UD: undetermined.

Table SIII. Study outcome variables according to International Classification of Functioning. Disability and Health (ICF) domain and code

Study	ICF domain	Code	Associated outcome variables
Agre et al. 1997 (44)	Muscle function; lower motor	B730: Muscle Power Functions	Knee extensor/flexor isokinetic torque Knee extensor/flexor total work Knee extensor isometric maximum voluntary contraction Knee flexor endurance time
Agre 1996 et al. (45)	Muscle function; lower motor	B730: Muscle Power Functions	Knee extensor/flexor isokinetic torque Knee extensor/flexor total work Knee extensor isometric maximum voluntary contraction Knee flexor endurance time
Bertelsen et al. 2009 (28)	Activity	D450: Walking	6-min walk test Timed sit to stand test
Brogardh et al. 2010 (46)	Muscle function Activity	B730: Muscle Power Functions B770: Gait pattern function D450: Walking	Knee extensor/flexor isokinetic torque Knee extensor isometric maximum voluntary contraction Timed Up and Go test 6-min walk test
Chan et al. 2003 (33)	Muscle function; lower motor	B730: Muscle Power Functions	Thumb maximum voluntary contraction Motor unit number
Da Silva et al. 2019 (37)	Muscle function Body function; mental and sensory Activity	B2802: Sensation of pain B4550: General physical endurance D450: Walking	Surface detected motor unit action potential. 10-metre walk test 2-min walk test Body pain index interference Body pain index severity Pittsburgh Sleep Quality Index
Davidson et al. 2009 (29)	Muscle function; lower motor Activity Mobility	B730: Muscle Power Functions B7402: Endurance of all muscles of the body D410: Changing body position	Fatigue Severity Scale Sit to stand Grip strength of dominant hand 10m shuttle walk test Hospital Anxiety and Depression Scale
Dean et al. 1991 (25)	Muscle function; lower motor Muscle function; cardiovascular Body function; mental and sensory	B4100: Heart rate B455: Exercise Tolerance Functions	Illness Perception Questionnaire Movement economy index Cardiorespiratory conditioning index Max heart rate Aerobic capacity VO2
Einarsson 1991 (35)	Muscle function; lower motor Activity	B4550: General physical endurance B730: Muscle Power Functions	Isometric flexion Isometric extension strength Isokinetic flexion strength Isokinetic extension strength Isokinetic extension strength Fatigue index Muscle biopsy
Ernstoff et al. 1996 (30)	Muscle function; lower motor Muscle function; cardiovascular Activity	B4100: Heart rate B730: Muscle Power Functions B4550: General physical endurance	Isokinetic concentric strength Isometric knee flexion Fatigue index Heart rate
Fillyaw et al. 1991 (36)	Muscle function; lower motor Muscle function; cardiovascular	B730: Muscle Power Functions B7402: Endurance of all muscles of the body	Maximum isometric torque Endurance integral
Jones et al. 1989 (47)	Muscle function; lower motor Muscle function; cardiovascular	B4100: Heart rate B420: Blood Pressure B4401: Respiratory rhythm B455: Exercise Tolerance Functions B4551: Aerobic Capacity	Resting heart rate Maximal heart rate Resting systolic blood pressure/Resting diastolic blood pressure Maximum systolic blood pressure/Maximum diastolic blood pressure Watts Exercise time Maximum expired volume, Maximum oxygen consumption Maximum carbon dioxide consumption Respiratory exchange ratio
Koopman et al. 2016 (3)	Muscle function; lower motor Muscle function; cardiovascular Body function; mental and sensory Participation	B134: Sleep functions B2802: Pain B730: Muscle power functions D450: Walking D455: Moving around	Fatigue assessed using 8-item subscale CIS20-F Sickness impact profile (SIP-68) Mobility control Social behaviour Mobility range Health Related Quality of Life (Short-form 36 (SF-36); Physical component summary, Mental component Summary 26). Pain Total mood disturbance Sleep disturbances Illness cognitions Coping General self -efficacy. Submaximal heart rate during exercise Maximal isokinetic voluntary torque of quadriceps muscles Timed Up and Go test 2-Min Walk test Actual daily physical activity level

Table SIII. Cont.			
Study	ICF domain	Code	Associated outcome variables
Kriz et al. 1992 (26)	Muscle function; upper motor	B4100: Heart Rate	Resting heart rate
	Muscle function; cardiovascular	B420: Blood pressure function	Max heart rate,
		B4401: Respiratory rhythm	Resting Blood Pressure
		B455: Exercise tolerance functions	Post exercise blood pressure
			VO ₂ max
			Min ventilation
			Respiratory exchange rate
			Respiratory rate
Murray et al. 2017 (4)	Muscle function; upper motor	B455: Exercise tolerance functions	Six-min Arm Test
	Body function; mental and	B4550: General physical	Fatigue Severity Scale
	sensory	endurance	Physical Activity Scale for Individuals with Physical Disabilities
Oncu et al. 2009 (48)	Body function; mental and	B4100: Heart rate	Fatigue severity scale/Fatigue intensity scale
	sensory	B455: Exercise tolerance functions	Quality of life
	Activity	B4550: General physical	Heart rate/Rhythm
		endurance	Max oxygen consumption (VO2) Carbon dioxide production (VCO_2)
Sharma et al. 2014 (32)	Body function; mental and	B4550: General physical	Fatigue severity scale
	sensory	endurance	2-min walking distance
	Activity Participation	D450: Walking	Patient-reported outcome measurement information system (PROMIS)
			Patient Health Questionnaire (PHQ-9)
Skough et al. 2008 (38)	Muscle function; lower motor	B730: Muscle Power Functions	Sit stand sit
	Activity	D410: Changing basic body position	Timed Up and Go test 6-min walk test
		D450: Walking	Muscle strength measurement by means of dynamic dynamometer
			Short-Form-36 questionnaire.
Spector et al. 1996 (39)	Muscle function; lower motor	B4550: General physical	Fatigue Severity Scale
	Muscle function; upper motor	endurance B730: Muscle Power Functions	Isometric and dynamic strength MRI
			Biopsies
Voorn et al. 2016 (49)	Muscle function; lower motor	B4401: Respiratory Rhythm	Muscle endurance
	Muscle function; cardiovascular		Muscle strength maximum voluntary contraction
		B4550: General physical endurance	Resting heart rate
		B730: Muscle Power Functions	Oxygen consumption at the anaerobic threshold
		B730. Muscle Power Fullctions	Submaximal VO2
			Submaximal respiratory exchange rate
			Submaximal rating of perceived exertion
Willen et al. 2001 (8)	Muscle function; lower motor	B4100: Heart rate	Peak load
	Muscle function; cardiovascular	B455: Exercise tolerance functions	
		B4550: General physical endurance	Peak heart rate
			Berg Balance Scale
		B755: Involuntary movement reaction functions	Visual analogue scale
			Pain scale
			Physical Activity Scale for the Elderly
			Nottingham Health Profile (NHP).

VO₂: oxygen consumption.

Table SIV. Quality assessment

	Sco	ring cr	iteria f	or qua	lity ass	sessme	ent											
First author	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Score (%)
Agre et al. 1996 (44)	Y	Υ	Υ	Υ	N	N	N	Υ	Υ	UD	Υ	Υ	Υ	UD	UD	UD	UD	53
Agre et al. 1997 (45)	Υ	Υ	Υ	Υ	N	N	N	Υ	Υ	UD	Υ	Υ	Υ	UD	UD	Υ	UD	59
Bertelsen et al. 2009 (28)	Υ	Υ	Υ	Υ	N	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	UD	N	UD	76
Brogardh et al. 2010 (46)	Υ	Υ	Υ	Υ	N	N	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	N	UD	N	71
Chan et al. 2003 (33)	Υ	Υ	Υ	Υ	N	N	N	Υ	Υ	UD	Υ	Υ	Υ	Υ	N	UD	N	59
Da Silva et al. 2019 (37)	Υ	Υ	Υ	Υ	N	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	N	Υ	UD	82
Davidson et al. 2009 (29)	Υ	Υ	Υ	Υ	N	Υ	N	Υ	Υ	Υ	Υ	Υ	Υ	Υ	UD	Υ	N	76
Dean et al. 1991 (25)	Υ	Υ	Υ	Υ	N	N	N	Υ	Υ	N	Υ	Υ	Υ	Υ	UD	N	UD	59
Einarsson 1991 (35)	Υ	Υ	Υ	Υ	N	Υ	N	Υ	Υ	Υ	Υ	Υ	Υ	N	N	Υ	UD	71
Ernstoff et al. 1996 (30)	Υ	Υ	Υ	Υ	Ν	Υ	Ν	Υ	Υ	UD	Υ	Υ	Υ	UD	N	Υ	N	65
Fillyaw et al. 1991 (36)	Υ	Υ	Υ	Υ	Ν	Υ	Υ	Υ	Υ	UD	Υ	Υ	Υ	Υ	UD	Υ	N	71
Jones et al. 1989 (47)	Υ	Υ	Υ	Υ	Ν	Υ	N	Υ	Υ	Υ	Υ	Υ	Υ	Υ	N	Υ	N	76
Koopman et al. 2016 (3)	Υ	Υ	Υ	Υ	N	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	UD	Υ	Υ	88
Kriz et al. 1992 (26)	Υ	Υ	Υ	Υ	Ν	Υ	N	Υ	Υ	Υ	Υ	Υ	Υ	Υ	UD	Υ	N	76
Murray et al. 2017 (4)	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	UD	Υ	Υ	Υ	Υ	UD	Υ	Υ	88
Oncu et al. 2009 (48)	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	UD	Υ	Υ	Υ	Υ	N	Υ	N	82
Sharma et al. 2014 (32)	Υ	Υ	Υ	Υ	N	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	N	Υ	N	82
Skough et al. 2008 (38)	Υ	Υ	Υ	Υ	N	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	UD	Υ	N	82
Spector et al. 1996 (39)	Υ	Υ	Υ	Υ	N	Ν	N	Υ	Υ	Υ	Υ	Υ	Υ	Υ	N	UD	N	65
Voorn et al. 2016 (49)	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	Υ	N	Υ	N	88
Willen et al. 2001 (8)	Υ	Υ	Υ	Υ	N	N	N	Υ	Υ	Υ	Υ	Υ	Υ	UD	N	UD	Ν	59

Y: yes; N: no; UD: undetermined

Table SV (A-Q). Sensitivity analyses

(A) Sensitivity analysis for combined interventions in the overall body function domain.

	Main analys	sis			Heteroger	neity		
Study	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	p-value	I ² (%)
Agre et al. 1996 (44)	0.307	0.195	0.420	<0.01	103.40	21	<0.01	80
Agre et al. 1997 (45)	0.297	0.183	0.411	< 0.01	106.35	21	< 0.01	80
Bertelsen et al. 2009 (28)	0.320	0.197	0.444	< 0.01	104.58	21	< 0.01	80
Brogardh et al. 2010 (46)	0.306	0.193	0.419	< 0.01	104.45	21	< 0.01	80
Chan et al. 2003 (33)	0.276	0.168	0.385	< 0.01	97.08	21	< 0.01	78
Da Silva et al. 2019a (37)	0.298	0.184	0.411	< 0.01	106.48	21	< 0.01	80
Da Silva et al. 2019b (37)	0.293	0.180	0.406	< 0.01	105.44	21	< 0.01	80
Davidson et al. 2009 (29)	0.295	0.179	0.411	< 0.01	105.84	21	< 0.01	80
Dean et al. 1991 (25)	0.284	0.172	0.397	< 0.01	100.09	21	< 0.01	79
Einarsson 1991 (35)	0.301	0.186	0.417	< 0.01	106.14	21	< 0.01	80
Ernstoff et al. 1996 (30)	0.252	0.150	0.353	< 0.01	96.23	21	< 0.01	78
Fillyaw et al. 1991 (36)	0.270	0.168	0.371	< 0.01	93.03	21	< 0.01	77
Jones et al. 1989 (47)	0.279	0.167	0.390	< 0.01	101.87	21	< 0.01	79
Koopman et al. 2016 (3)	0.324	0.201	0.447	< 0.01	100.63	21	< 0.01	79
Kriz et al. 1992 (26)	0.296	0.183	0.408	< 0.01	106.08	21	< 0.01	80
Murray et al. 2017 (4)	0.290	0.177	0.403	< 0.01	106.50	21	< 0.01	80
Oncu et al. 2009 (48)	0.291	0.189	0.392	< 0.01	77.92	21	< 0.01	73
Sharma et al. 2014 (32)	0.287	0.174	0.399	< 0.01	103.48	21	< 0.01	80
Skough et al. 2008 (38)	0.289	0.178	0.401	< 0.01	104.76	21	< 0.01	80
Spector et al. 1996 (39)	0.303	0.190	0.415	< 0.01	105.87	21	< 0.01	80
Voorn et al. 2016 (49)	0.302	0.189	0.414	< 0.01	106.12	21	< 0.01	80
Willen et al. 2001 (8)	0.315	0.197	0.433	< 0.01	105.17	21	< 0.01	80
Murray et al. 2016 (4)	0.323	0.214	0.432	< 0.01	90.40	21	< 0.01	77

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(B) Sensitivity analysis for aerobic interventions in the overall body function domain

	Main analys	is			Heterogene	eity		
Study	Hedge's g	95% LB	95% UB	p-value	Q df	<i>p</i> -value	I ² (%)	
Dean et al. 1991 (25)	0.489	0.210	0.768	<0.01	27.598	4	<0.01	85
Jones et al. 1989 (47)	0.531	0.211	0.850	< 0.01	29.530	4	< 0.01	86
Kriz et al. 1992 (26)	0.580	0.305	0.854	< 0.01	22.930	4	< 0.01	83
Murray et al. 2017 (4)	0.570	0.278	0.862	< 0.01	25.326	4	< 0.01	84
Oncu et al. 2009a (48)	0.374	0.216	0.532	< 0.01	9.319	4	0.05	57
Oncu et al. 2009b (48)	0.502	0.224	0.780	< 0.01	28.994	4	< 0.01	86

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(C) Sensitivity analysis for mixed interventions in the overall body function domain

Study	Main analys		Heteroger	eity				
	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)
Bertelsen et al. 2009 (28)	0.238	0.045	0.431	0.02	28.272	5	<0.01	82
Davidson et al. 2009 (29)	0.199	0.037	0.362	0.02	26.195	5	< 0.01	81
Ernstoff et al. 1996 (30)	0.138	0.027	0.248	0.01	11.333	5	0.05	56
Koopman et al. 2016 (3)	0.248	0.055	0.441	0.01	27.272	5	< 0.01	82
Voorn et al. 2016 (49)	0.237	0.065	0.410	0.01	28.104	5	< 0.01	82
Willen et al. 2001 (8)	0.267	0.116	0.418	< 0.01	18.846	5	< 0.01	73

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(D) Sensitivity analysis for strengthening interventions in the overall body function domain

	Main analys	is			Heteroger	eity		
Study	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)
Agre et al. 1996 (44)	0.347	0.127	0.566	<0.01	26.128	8	<0.01	69
Agre et al. 1997 (45)	0.309	0.078	0.539	0.01	29.999	8	< 0.01	73
Brogargh et al. 2010 (46)	0.343	0.122	0.563	< 0.01	27.544	8	< 0.01	71
Chan et al. 2002 (33)	0.241	0.049	0.433	0.01	20.349	8	0.01	61
Da Silva et al. 2019a (37)	0.312	0.086	0.538	0.01	30.089	8	< 0.01	73
Da Silva et al. 2019b (37)	0.292	0.069	0.515	0.01	29.131	8	< 0.01	73
Einarsson 1991 (35)	0.330	0.086	0.574	0.01	29.358	8	< 0.01	73
Fillyaw et al. 1991 (36)	0.234	0.073	0.395	< 0.01	16.709	8	0.03	52
Skough et al. 2008 (38)	0.330	0.110	0.550	< 0.01	29.318	8	< 0.01	73
Spector et al. 1996 (39)	0.326	0.106	0.546	< 0.01	29.609	8	< 0.01	73

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(E) Sensitivity analysis for all interventions in the lower limb component of the overall body function domain

	Main analys	is			Heterogen	eity		
Study	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)
Agre et al. 1996 (44)	0.185	0.064	0.306	<0.01	24.554	11	0.01	55
Agre et al. 1997 (45)	0.174	0.053	0.295	< 0.01	25.163	11	< 0.01	56
Brogargh et al. 2010 (46)	0.185	0.064	0.306	< 0.01	24.952	11	< 0.01	56
Dean et al. 1991 (25)	0.147	0.047	0.247	< 0.01	23.780	11	0.01	54
Einarsson 1991 (35)	0.178	0.054	0.301	< 0.01	25.919	11	< 0.01	58
Ernstoff et al. 1996 (30)	0.197	0.050	0.343	< 0.01	25.754	11	< 0.01	57
Fillyaw et al. 1991 (36)	0.140	0.050	0.230	< 0.01	10.572	11	0.48	0
Jones et al. 1989 (47)	0.163	0.044	0.282	< 0.01	24.073	11	0.01	54
Koopman et al. 2016 (3)	0.210	0.067	0.354	< 0.01	25.930	11	< 0.01	58
Skough et al. 2008 (38)	0.182	0.062	0.302	< 0.01	25.793	11	< 0.01	57
Spector et al. 1996 (39)	0.175	0.057	0.294	< 0.01	25.741	11	< 0.01	57
Voorn et al. 2016 (49)	0.176	0.049	0.303	< 0.01	25.494	11	< 0.01	57
Willen et al. 2001 (8)	0.225	0.105	0.344	<0.01	22.710	11	0.02	52

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(F) Sensitivity analysis for mixed interventions in the lower limb component of the overall body function domain

Study	Main analys	is			Heteroge	neity		
	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)
Dean et al. 1991 (25)	0.114	0.001	0.226	0.05	2.842	3	0.42	0
Ernstoff et al. 1996 (30)	0.134	-0.062	0.330	0.18	4.534	3	0.21	34
Koopman et al. 2016 (3)	0.162	-0.027	0.351	0.09	5.259	3	0.15	43
Voorn et al. 2016 (49)	0.127	-0.028	0.281	0.11	4.574	3	0.21	34
Willen et al. 2001 (8)	0.203	0.061	0.345	0.01	2.335	3	0.51	0

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(G) Sensitivity analysis for strengthening interventions in the lower limb component of the overall body function domain

Study	Main analys	is			Heteroger	eity		
	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)
Agre et al. 1996 (44)	0.296	0.014	0.577	0.04	16.733	5	0.01	70
Agre et al. 1997 (45)	0.235	-0.049	0.519	0.10	17.887	5	< 0.01	72
Brogargh et al. 2010 (46)	0.291	0.011	0.571	0.04	17.280	5	< 0.01	71
Einarsson 1991 (35)	0.275	-0.042	0.592	0.09	18.597	5	< 0.01	73
Fillyaw et al. 1991 (36)	0.123	0.001	0.244	0.05	3.249	5	0.66	0
Skough et al. 2008 (38)	0.267	-0.001	0.536	0.05	18.368	5	< 0.01	73
Spector et al. 1996 (39)	0.229	-0.025	0.482	0.08	18.409	5	< 0.01	73

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(H) Sensitivity analysis for all interventions in the non-lower limb component of the overall body function domain

Study	Main analys	is			Heterogen	eity		
	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)
Chan et al. 2002 (2003)	0.428	0.283	0.574	<0.01	16.440	3	<0.01	82
Ernstoff et al. 1996 (30)	0.266	0.083	0.449	< 0.01	7.701	3	0.05	61
Kriz et al. 1992 (26)	0.474	0.319	0.629	< 0.01	18.092	3	< 0.01	83
Murray et al. 2017 (4)	0.698	0.485	0.912	< 0.01	10.354	3	0.02	71
Spector et al. 1996 (39)	0.511	0.377	0.644	< 0.01	14.170	3	< 0.01	79

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(I) Sensitivity analysis for all interventions in the cardiovascular component of the overall body function domain

Study	Main analys	is			Heteroger	neity		
	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)
Dean et al. 1991 (25)	0.077	-0.078	0.232	0.33	21.683	6	<0.01	72
Jones et al. 1989 (47)	0.060	-0.103	0.223	0.47	19.164	6	< 0.01	69
Koopman et al. 2016 (3)	0.184	-0.010	0.378	0.06	25.032	6	< 0.01	76
Kriz et al. 1992 (26)	0.104	-0.052	0.260	0.19	25.848	6	< 0.01	77
Oncu et al. 2009a (48)	0.103	-0.041	0.247	0.16	20.044	6	< 0.01	70
Oncu et al. 2009b (48)	0.136	-0.011	0.284	0.07	24.462	6	< 0.01	75
Voorn et al. 2016 (49)	0.078	-0.087	0.242	0.36	25.480	6	< 0.01	76
Willen et al. 2001 (8)	0.178	0.029	0.327	0.02	17.691	6	0.01	66

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(J) Sensitivity analysis for aerobic interventions in the cardiovascular component of the overall body function domain

Study	Main analys	is			Heteroger	neity		I ² (%) 72 74			
	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)			
Dean et al. 1991 (29)	0.319	-0.008	0.645	0.06	10.675	3	0.01	72			
Jones et al. 1989 (47)	0.366	-0.056	0.789	0.09	11.342	3	0.01	74			
Kriz et al. 1992 (26)	0.461	0.125	0.798	0.01	7.664	3	0.05	61			
Oncu et al. 2009a (48)	0.297	0.047	0.548	0.02	8.217	3	0.04	63			
Oncu et al. 2009b (48)	0.441	0.171	0.711	< 0.01	9.461	3	0.02	68			

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(K) Sensitivity analysis for mixed interventions in the cardiovascular component of the overall body function domain

	Main analysi	s			Heterogen	eity		
Study	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)
Koopman et al. 2016 (3)	-0.008	-0.283	0.268	0.96	2.725	1	0.10	63
Voorn et al. 2016 (49)	-0.092	-0.299	0.115	0.38	0.696	1	0.40	0
Willen et al. 2001 (8)	0.095	-0.083	0.273	0.30	0.238	1	0.63	0

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(L) Sensitivity analysis for all interventions in the mental and sensory component of the overall body function domain

	Main analys	is			Heterogeneity				
Study	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)	
Bertelsen et al. 2009 (28)	0.364	0.200	0.529	<0.01	36.612	8	<0.01	78	
Da Silva et al. 2019a (37)	0.249	0.140	0.358	< 0.01	40.391	8	< 0.01	80	
Da Silva et al. 2019b (37)	0.235	0.126	0.344	< 0.01	39.466	8	< 0.01	80	
Davidson et al. 2009 (29)	0.221	0.118	0.323	< 0.01	39.897	8	< 0.01	80	
Dean et al. 1991 (25)	0.240	0.134	0.346	< 0.01	38.997	8	< 0.01	79	
Koopman et al. 2016 (3)	0.352	0.200	0.505	< 0.01	34.852	8	< 0.01	77	
Murray et al. 2017 (4)	0.283	0.180	0.386	< 0.01	40.270	8	< 0.01	80	
Oncu et al. 2009a (48)	0.244	0.140	0.348	< 0.01	17.466	8	0.03	54	
Oncu et al. 2009b (48)	0.234	0.127	0.340	< 0.01	32.348	8	< 0.01	75	
Sharma et al. 2014 (32)	0.209	0.125	0.294	< 0.01	38.771	8	< 0.01	79	

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(M) Sensitivity analysis for aerobic interventions in the mental and sensory component of the overall body function domain

Study	Main analys		Heterogeneity					
	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)
Dean et al. 1991 (25)	0.763	0.191	1.335	0.01	10.229	2	0.01	80
Murray et al. 2017 (4)	0.928	0.579	1.277	< 0.01	3.531	2	0.17	43
Oncu et al. 2009a (48)	0.556	0.151	0.960	0.01	4.022	2	0.13	50
Oncu et al. 2009b (48)	0.684	0.025	1.344	0.04	10.634	2	< 0.01	81

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(N) Sensitivity analysis for mixed interventions in the mental and sensory component of the overall body function domain

Study	Main analys	is		Heterogeneity					
	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)	
Bertelsen et al. 2009 (28)	0.268	0.036	0.500	0.02	4.472	2	0.11	55	
Davidson et al. 2009 (29)	0.163	0.049	0.277	< 0.01	2.705	2	0.26	26	
Koopman et al. 2016 (3)	0.271	0.068	0.473	0.01	3.685	2	0.16	46	
Sharma et al. 2014 (32)	0.171	0.080	0.262	< 0.01	2.233	2	0.33	10	

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(O) Sensitivity analysis for all interventions in the combined activity and participation domain

Study	Main analys	is		Heterogeneity					
	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)	
Bertelsen et al. 2009 (28)	0.125	0.054	0.196	<0.01	2.100	8	0.98	0	
Brogardh et al. 2010 (46)	0.147	0.092	0.203	< 0.01	1.455	8	0.99	0	
Da Silva et al. 2019a (37)	0.143	0.088	0.198	< 0.01	2.711	8	0.95	0	
Da Silva et al. 2019b (37)	0.141	0.086	0.196	< 0.01	2.402	8	0.97	0	
Davidson et al. 2009 (29)	0.151	0.091	0.211	< 0.01	2.294	8	0.97	0	
Koopman et al. 2016 (3)	0.147	0.083	0.212	< 0.01	2.669	8	0.95	0	
Murray et al. 2017 (4)	0.140	0.083	0.197	< 0.01	2.634	8	0.96	0	
Sharma et al. 2014 (32)	0.142	0.087	0.197	< 0.01	2.578	8	0.96	0	
Skough et al. 2008 (38)	0.144	0.089	0.200	< 0.01	2.622	8	0.96	0	
Willen et al. 2001 (8)	0.143	0.087	0.198	< 0.01	2.723	8	0.95	0	

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(P) Sensitivity analysis for mixed interventions in the combined activity and participation domain

Study	Main analys	is		Heterogeneity				
	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)
Bertelsen et al. 2009 (28)	0.124	0.043	0.204	<0.01	0.355	3	0.95	0
Davidson et al. 2009 (29)	0.155	0.090	0.221	< 0.01	0.441	3	0.93	0
Koopman et al. 2016 (3)	0.152	0.080	0.223	< 0.01	0.841	3	0.84	0
Sharma et al. 2014 (32)	0.14396	0.085	0.203	< 0.01	0.795	3	0.85	0
Willen et al. 2001 (8)	0.145	0.085	0.204	< 0.01	0.938	3	0.82	0

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound.

(Q) Sensitivity analysis for strengthening interventions in the combined activity and participation domain

Study	Main analys	is		Heterogeneity					
	Hedge's g	95% LB	95% UB	<i>p</i> -value	Q	df	<i>p</i> -value	I ² (%)	
Brogargh et al. 2010 (46)	0.142	-0.127	0.411	0.30	0.441	2	0.80	0	
Da Silva et al. 2019a (37)	0.065	-0.181	0.310	0.61	1.281	2	0.53	0	
Da Silva et al. 2019b (37)	0.023	-0.223	0.270	0.85	0.476	2	0.79	0	
Skough et al. 2008 (38)	0.066	-0.212	0.344	0.64	1.297	2	0.52	0	

95% CI: 95% confidence interval; LB: lower bound; UB: upper bound. Due to low study number, sensitivity analyses could not be completed for aerobic interventions in the lower limb component of the body function domain (n=1), any individual interventions in the non-lower limb component of the body function domain (n ranging from 1 to 2), strengthening in the mental and sensory component of the body function domain (n = 2), and aerobic interventions in the combined activity and participation domain (n=1).

Intervention type										
		Hedges's g	Lower limit	Upper limit	P-Value					Rela we
K·	iriz, et al. 1992 (26)	0.177	-0.028	0.381	0.09			 		
M	furray, et al. 2017 (4)	0.237	0.044	0.430	0.02					
Jc	ones, et al. 1989 (47)	0.436	0.254	0.619	0.00			-		
0	ncu, et al. 2009B (48)	0.548	0.200	0.895	0.00			-	⊢ ∣	
D	ean, et al. 1991 (25)	0.613	0.322	0.903	0.00			-	-	
О	ncu, et al. 2009A (48)	1.186	0.837	1.534	0.00				_	
Aerobic	, ,	0.506	0.263	0.749	0.00				▶	
W	Villen, et al. 2001 (8)	-0.050	-0.201	0.100	0.51			.		
K	Loopman, et al. 2016 (3)	0.117	0.005	0.229	0.04					
В	ertelsen, et al. 2009 (28)	0.162	0.040	0.285	0.01					
D	avidson, et al. 2009 (29)	0.346	0.092	0.599	0.01					
E:	rnstoff, et al. 1996 (30)	0.550	0.356	0.744	0.00			-	⊢	
SI	harma, et al. 2014 (32)	0.651	0.041	1.262	0.04					
Mixed		0.237	0.065	0.410	0.01					
A	gre, et al. 1996 (44)	-0.007	-0.289	0.275	0.96			-4-		
	rogargh, et al. 2010 (46)	0.003	-0.327	0.334	0.98			_ _		
SI	kough, et al. 2008 (38)	0.056	-0.406	0.519	0.81			-		
	pector, et al. 1996 (39)	0.092	-0.387	0.572	0.71					
-	inarsson, et al. 1991 (35)		-0.024	0.387	0.08			-		
	a Silva, et al. 2019A (37)		-0.122	0.656	0.18			+=-	.	
	a Silva, et al. 2019B (37)		0.058	0.828	0.02				_	
	han, et al. 2002 (33)	0.719	0.411	1.026	0.00			1 =	-	
F.	illyaw, et al. 1991 (36)	1.595	0.871	2.319	0.00			- 1		
Strengthening	, ,	0.309	0.078	0.539	0.01					
Overall		0.322	0.202	0.443	0.00			•		
						-2.50	-1.25	0.00	1.25	2.50

A) Body function overall

Group by Intervention type	Study name	Statistics for each study					Hed	ges's g and 9	5% CI	
		Hedges's g	Lower limit	Upper limit	P-Value					Relativ weigh
	Jones, et al. 1989 (47)	0.585	-0.036	1.205	0.06			\vdash	-	100.
Aerobic		0.585	-0.036	1.205	0.06					
	Willen, et al. 2001 (8)	0.004	-0.175	0.183	0.97			-#-		37
	Koopman, et al. 2016 (3)	0.125	-0.141	0.391	0.36			+		23
	Ernstoff, et al. 1996 (30)	0.192	0.004	0.380	0.05			-		35.:
	Dean, et al. 1991 (25)	0.733	-0.042	1.508	0.06					3.
Mixed		0.127	-0.028	0.281	0.11			•		
	Agre, et al. 1996 (44)	-0.007	-0.279	0.265	0.96			-		21.
	Brogargh, et al. 2010 (46)	0.003	-0.295	0.301	0.98			-+-		20.
	Skough, et al. 2008 (38)	0.054	-0.395	0.504	0.81					15.
	Einarsson, et al. 1991 (35)	0.174	-0.023	0.372	0.08			 -		23
	Spector, et al. 1996 (39)	0.336	-0.417	1.089	0.38			- -		9.3
	Fillyaw, et al. 1991 (36)	1.557	0.850	2.264	0.00					9.
Strengthening		0.235	-0.049	0.519	0.10					
Overall		0.171	0.039	0.304	0.01			•		
						2.50	1.25	0.00	1.25	2.50

B) Body function lower limb

Group by Intervention type	Study name	Statistics for each study					Hedg	ges's g and 95	ad 95% CI		
	I	Hedges's g	Lower limit		<i>P</i> -Value					Relative weight	
	Oncu, et al. 2009 B (48)	-0.245	-0.919	0.430	0.48		I—			11.07	
	Kriz, et al. 1992 (26)	0.142	-0.080	0.364	0.21			-		27.78	
	Jones, et al. 1989 (47)	0.422	0.231	0.612	0.00			-	⊢	29.19	
	Dean, et al. 1991 (25)	0.582	0.215	0.949	0.00			-	━	21.08	
	Oncu, et al. 2009 A (48)	1.053	0.370	1.736	0.00			-	-	10.88	
Aerobic		0.373	0.100	0.646	0.01				▶		
	Willen, et al. 2001 (8)	-0.160	-0.421	0.101	0.23					62.90	
	Koopman, et al. 2016 (3)	0.023	-0.317	0.362	0.90					37.10	
Mixed		-0.092	-0.299	0.115	0.38			*			
Overall		0.078	-0.087	0.242	0.36			•			
						-2.00	-1.00	0.00	1.00	2.00	

Favours impairment

Favours improvement

C) Body function cardiovascular